PATENT COOPERATION TREATY

PCT

REC'D 22 MAY 2006
WIPO PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2159.045PC01--	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2005/002535	International filing date *(day/month/year)* 28.01.2005	Priority date *(day/month/year)* 30.01.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K38/17 C07K16/28 A61P25/00 A61P25/28		
Applicant BIOGEN IDEC MA INC. ET AL.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 13 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.01.2006	12.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Mateo Rosell, A.M. Telephone No. +49 30 25901-319

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/002535

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-6, 8-18	as originally filed
7	received on 27.01.2006 with letter of 24.01.2006

Sequence listings part of the description, Pages

1-12	received on 27.01.2006 with letter of 24.01.2006

Claims, Numbers

1-23	as originally filed

Drawings, Sheets

1/3-3/3	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-23 with respect to industrial applicability,claim 1 partially and claims 6-9,17,18 with respect to PCT Rule 13ter, Rule 5.2 and Art. 17(2)(a) PCT.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 1-23 with respect to industrial applicability, claim 1 partially and claims 6-9, 17,18 with respect to PCT Rule 13ter, Rule 5.2 and Art. 17(2)(a) PCT.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/002535

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5,10-16,19-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5,10-16,19-23
Industrial applicability (IA)	Yes:	Claims	-
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment* on 24.01.2006

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Re Item I
Basis of the report

Reference is made to the following documents:

D1: WO03031462 (YALE UNIVERSITY). 17.04.2003.
D2: LI ET AL., SOCIETY FOR NEUROSCIENCE ABSTRACTS, 2003, page ABSTRNO67803.
D3: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2003, LI M ET AL: Database accession no. PREV200400194121
D4: GRANDPRE ET AL., NATURE, 2002, vol. 417: 547-551
D5: OERTLE T ET AL: J. NEUROSCIENCE, 2003, vol. 23(13): 5393-5406
D6: DOMENICONE ET AL., NEURON, 2002, vol 35: 283-290

Re Item II
Priority

It should be noted that the documents D7-D8 indicated in the search report as 'PX documents' have not been taken into consideration for the evaluation of novelty and inventive step, since the priority of the present application had not been furnished in due time. Nevertheless, the Applicant should take into account that for a posterior European phase, this documents might be relevant.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

I. Claims 1-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

II. The present claim 1 relates to an extremely large number of possible NgR1 antagonists not yet discovered neither explored by the applicant. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of such NgR1 antagonists. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claim 1 (PCT Guidelines 9.19 and 9.23).

The search of claim 1 was restricted to the claimed NgR1 antagonists which appear to be supported, namely Nogo fragments and anti-NgR1 antibodies (see claims 6-9,15-18), and those already known NgR1 inhibitors such as Ompg and MAG.

III. The specific sequences of claim(s) 6-9, 17,18 have, according to PCT Rule 13ter.1.c, not been searched since the Sequence Listing as present in the description does not comply with WIPO Standard ST 25 prescribed in the administrative instructions under Rule 5.2. The Sequence Listing has been furnished neither in paper form nor in machine readable form as provided for in the same instructions and the applicant has not remedied the disclosed deficiencies within the time limit fixed in the invitation pursuant to PCT Rule 13ter.1.a.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses Nogo fragments which antagonize Nogo (Pep 1, residues 1-25 of the extracellular domain, Pep 2, 11-35, Pep 3, 21-45, Pep 2-41, Pep 140, soluble hNogo-A(1055-1120) and SEQ.ID.N.7-53) for use in a method for treating a central nervous system disease, disorder or injury (by decreasing the inhibition of axonal growth) (see pages 5, line 11 - page 8, line 19, table 2 and examples 1-23)

D2 describes an anti-NgR1 antibody, 7E11, an IgGa molecule that recognizes a unique

epitope of 16 amino acid residues located on a LRR domain of rat NgR1 which promotes neurite outgrowth in primary rat DRG neurons (see abstract).

The subject-matter of claim 1 differs from this known D1 and D2 in that the NgR1 antagonist used in the present application, namely sNgR(310)Fc, significantly increased dopaminergic neural survival in the substantia nigra after striatal 6-OHDA lesioning, whereas in D1 and D2 the NgR1 antagonist used reduced growth cone collapse in chick DRG explant cultures and promote neurite outgrowth chick DRG explant cultures (see example 16 of D1) and promote neurite outgrowth in primary rat DRG neurons (see abstract of D2) while in the preent application.

The subject-matter of claims 1-5,10-16,19-23 (see item III) is therefore new (Article 33(2) PCT).

Inventive step

The problem to be solved by the present invention may be regarded as the provision of methods to treating conditions involving dopaminergic neuronal degeneration.

The solution to this problem proposed in claim 1 of the present application is the provision and administration of NgR1 antagonists in mammals displaying signs or symptoms of dopaminergic neuronal degeneration.

This solution cannot be considered inventive for the following reasons:

Nogo fragments and antibodies which antagonize NgR1 have been already described in the prior art (see for example D1 and D2, see above, and corresponding passages cited in the search report of documents D3-D5). Moreover, D1 intends the use of Nogo fragments in a method for treating a central nervous system disease, disorder or injury (see page 8, lines 3-10). D4 suggets the therapeutic use of NgR1 antagonist(s) in clinical conditions such as spinal cord injury, brain trauma, white matter stroke or chronic progressive multiple sclerosis. Finally, D6 suggests as well the use of NgR1 antagonists for the development of therapies for spinal cord and CNS injury (see abstract, page 284, left-hand column,

paragraph 1 to page 286, right-hand column, paragraph 2 and page 288, right-hand column, last paragraph to page 289, left-hand column, paragraph 1).

In view of the above paragraph, the skilled person would be prompted to develop therapies for CNS disorders or injuries using NgR1 antagonists as taught in D1-D6. Therefore the subject-matter of claims 1-5,10-16,19-23 cannot be considered as involving an inventive step under the requirements of Art. 33(3) PCT.

Industrial applicability

For the assessment of the present claims 1-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/014311	19.02.2004	07.08.2003	10.08.2002

Li et al., 2004. JBC, vol 279(42): 43780-43788. (15.10.2004)

Re Item VII
Certain defects in the international application

This ISA adopts the view that the specification only demonstrates a significant increased dopaminergic neural survival in the substantia nigra when the NgR1 antagonist sNgR(310)Fc is infused into the striatum after striatal 6-OHDA lesioning.

This ISA set out to examine the plausibility of verifying that all claimed soluble forms, antibodies, antibody fragments, Ig-fusion proteins, monoclonal antibodies and Nogo fragments (when restricted to those disclosed in claims 6-9,15,17-18) and concludes that this undertaking constitutes an undue burden for the skilled person seeking to perform the claimed invention and does not fulfil the requirements of Art. 5 PCT.

Re Item VIII

Certain observations on the international application

I. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

This ISA considers that the second medical use claim defines the therapeutic application of the NgR1 antagonist by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition.
The claims should introduce a list of pathological conditions (diseases) cited in the application, or it sould be shown that means are available which would allow the skilled person to recognize which additional condition(s) would fall within the functional definition.

Soluble Nogo Receptor-1 Polypeptides

[0034] In some embodiments of the invention, the antagonist is a soluble Nogo receptor-1 polypeptide (Nogo receptor-1 is also variously referred to as "Nogo receptor," "NogoR," "NogoR-1," "NgR," and "NgR-1"). Full-length Nogo receptor-1 consists of a signal sequence, a N-terminus region (NT), eight leucine rich repeats (LRR), a LRRCT region (a leucine rich repeat domain C-terminal of the eight leucine rich repeats), a C-terminus region (CT) and a GPI anchor. The sequences of human and rat Nogo receptors are shown in Table 1.

Table 1. Sequences of Human and Rat Nogo receptor-1 Polypeptides

Human Nogo receptor SEQ ID NO: 1	MKRASAGGSRLLAWVLWLQAWQVAAPCPGACVCYNEPKVTT SCPQQGLQAVPVGIPAASQRIFLHGNRISHVPAASFRACRNLTIL WLHSNVLARIDAAAFTGLALLEQLDLSDNAQLRSVDPATFHGL GRLHTLHLDRCGLQELGPGLFRGLAALQYLYLQDNALQALPDD TFRDLGNLTHLFLHGNRISSVPERAFRGLHSLDRLLLHQNRVAH VHPHAFRDLGRLMTLYLFANNLSALPTEALAPLRALQYLRLND NPWVCDCRARPLWAWLQKFRGSSSEVPCSLPQRLAGRDLKRLA ANDLQGCAVATGPYHPIWTGRATDEEPLGLPKCCQPDAADKA
Rat Nogo receptor SEQ ID NO: 2	MKRASSGGSRLPTWVLWLQAWRVATPCPGACVCYNEPKVTTS RPQQGLQAVPAGIPASSQRIFLHGNRISYVPAASFQSCRNLTILW LHSNALAGIDAAAFTGLTLLEQLDLSDNAQLRVVDPTTFRGLGH LHTLHLDRCGLQELGPGLFRGLAALQYLYLQDNNLQALPDNTF RDLGNLTHLFLHGNRIPSVPEHAFRGLHSLDRLLLHQNHVARVH PHAFRDLGRLMTLYLFANNLSMLPAEVLVPLRSLQYLRLNDNP WVCDCRARPLWAWLQKFRGSS SGVPSNLPQRLAGRDLKRLATS DLEGCAVASGPFRPFQTNQLTDEELLGLPKCCQPDAADKA

[0035] Soluble Nogo receptor polypeptides used in the methods of the invention comprise an NT domain; 8 LRRs and an LRRCT domain and lack a signal sequence and a functional GPI anchor (*i.e.*, no GPI anchor or a GPI anchor that fails to efficiently associate to a cell membrane). Suitable polypeptides include, for example, amino acids 26 – 310 (SEQ ID NO: 3) and 26 – 344 (SEQ ID NO: 4) of the human Nogo receptor and amino acids 27 – 310 (SEQ ID NO: 5) and 27 – 344 (SEQ ID NO: 6) of the rat Nogo receptor (Table 2). Additional polypeptides which may be used in the methods of the invention are described, for example, in International Patent Applications PCT/US02/32007 and PCT/US03/25004.

SEQUENCE LISTING

<110> BIOGEN IDEC MA INC.
YALE UNIVERSITY
RELTON, JANE K.
ENGBER, THOMAS M.
STRITTMATTER, STEPHEN M.

<120> TREATMENT OF CONDITIONS INVOLVING DOPAMINERGIC NEURONAL DEGENERATION USING NOGO RECEPTOR ANTAGONISTS

<130> A222 PCT

<150> 60/540,798
<151> 2004-01-30

<160> 22

<170> PatentIn Ver. 3.3

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<212> PRT
<213> Homo sapiens

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20 25 30

Cys Tyr Asn Glu Pro Lys Val Thr Thr Ser Cys Pro Gln Gln Gly Leu
35 40 45

Gln Ala Val Pro Val Gly Ile Pro Ala Ala Ser Gln Arg Ile Phe Leu
50 55 60

His Gly Asn Arg Ile Ser His Val Pro Ala Ala Ser Phe Arg Ala Cys
65 70 75 80

Arg Asn Leu Thr Ile Leu Trp Leu His Ser Asn Val Leu Ala Arg Ile
85 90 95

Asp Ala Ala Ala Phe Thr Gly Leu Ala Leu Leu Glu Gln Leu Asp Leu
100 105 110

Ser Asp Asn Ala Gln Leu Arg Ser Val Asp Pro Ala Thr Phe His Gly
115 120 125

Leu Gly Arg Leu His Thr Leu His Leu Asp Arg Cys Gly Leu Gln Glu
130 135 140

Leu Gly Pro Gly Leu Phe Arg Gly Leu Ala Ala Leu Gln Tyr Leu Tyr
145 150 155 160

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Leu Gln Asp Asn Ala Leu Gln Ala Leu Pro Asp Asp Thr Phe Arg Asp
                165                 170                 175

Leu Gly Asn Leu Thr His Leu Phe Leu His Gly Asn Arg Ile Ser Ser
            180                 185                 190

Val Pro Glu Arg Ala Phe Arg Gly Leu His Ser Leu Asp Arg Leu Leu
        195                 200                 205

Leu His Gln Asn Arg Val Ala His Val His Pro His Ala Phe Arg Asp
    210                 215                 220

Leu Gly Arg Leu Met Thr Leu Tyr Leu Phe Ala Asn Asn Leu Ser Ala
225                 230                 235                 240

Leu Pro Thr Glu Ala Leu Ala Pro Leu Arg Ala Leu Gln Tyr Leu Arg
                245                 250                 255

Leu Asn Asp Asn Pro Trp Val Cys Asp Cys Arg Ala Arg Pro Leu Trp
            260                 265                 270

Ala Trp Leu Gln Lys Phe Arg Gly Ser Ser Ser Glu Val Pro Cys Ser
        275                 280                 285

Leu Pro Gln Arg Leu Ala Gly Arg Asp Leu Lys Arg Leu Ala Ala Asn
    290                 295                 300

Asp Leu Gln Gly Cys Ala Val Ala Thr Gly Pro Tyr His Pro Ile Trp
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Gln Pro Asp Ala Ala Asp Lys Ala
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            20                  25                  30

Cys Tyr Asn Glu Pro Lys Val Thr Thr Ser Arg Pro Gln Gln Gly Leu
        35                  40                  45

Gln Ala Val Pro Ala Gly Ile Pro Ala Ser Ser Gln Arg Ile Phe Leu
    50                  55                  60

His Gly Asn Arg Ile Ser Tyr Val Pro Ala Ala Ser Phe Gln Ser Cys
65                  70                  75                  80
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Arg Asn Leu Thr Ile Leu Trp Leu His Ser Asn Ala Leu Ala Gly Ile
85 90 95

Asp Ala Ala Ala Phe Thr Gly Leu Thr Leu Leu Glu Gln Leu Asp Leu
100 105 110

Ser Asp Asn Ala Gln Leu Arg Val Val Asp Pro Thr Thr Phe Arg Gly
115 120 125

Leu Gly His Leu His Thr Leu His Leu Asp Arg Cys Gly Leu Gln Glu
130 135 140

Leu Gly Pro Gly Leu Phe Arg Gly Leu Ala Ala Leu Gln Tyr Leu Tyr
145 150 155 160

Leu Gln Asp Asn Asn Leu Gln Ala Leu Pro Asp Asn Thr Phe Arg Asp
165 170 175

Leu Gly Asn Leu Thr His Leu Phe Leu His Gly Asn Arg Ile Pro Ser
180 185 190

Val Pro Glu His Ala Phe Arg Gly Leu His Ser Leu Asp Arg Leu Leu
195 200 205

Leu His Gln Asn His Val Ala Arg Val His Pro His Ala Phe Arg Asp
210 215 220

Leu Gly Arg Leu Met Thr Leu Tyr Leu Phe Ala Asn Asn Leu Ser Met
225 230 235 240

Leu Pro Ala Glu Val Leu Val Pro Leu Arg Ser Leu Gln Tyr Leu Arg
245 250 255

Leu Asn Asp Asn Pro Trp Val Cys Asp Cys Arg Ala Arg Pro Leu Trp
260 265 270

Ala Trp Leu Gln Lys Phe Arg Gly Ser Ser Ser Gly Val Pro Ser Asn
275 280 285

Leu Pro Gln Arg Leu Ala Gly Arg Asp Leu Lys Arg Leu Ala Thr Ser
290 295 300

Asp Leu Glu Gly Cys Ala Val Ala Ser Gly Pro Phe Arg Pro Phe Gln
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Gln Pro Asp Ala Ala Asp Lys Ala
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            20                  25                  30

Ala Ser Gln Arg Ile Phe Leu His Gly Asn Arg Ile Ser His Val Pro
        35                  40                  45

Ala Ala Ser Phe Arg Ala Cys Arg Asn Leu Thr Ile Leu Trp Leu His
    50                  55                  60

Ser Asn Val Leu Ala Arg Ile Asp Ala Ala Ala Phe Thr Gly Leu Ala
65                  70                  75                  80

Leu Leu Glu Gln Leu Asp Leu Ser Asp Asn Ala Gln Leu Arg Ser Val
                85                  90                  95

Asp Pro Ala Thr Phe His Gly Leu Gly Arg Leu His Thr Leu His Leu
            100                 105                 110

Asp Arg Cys Gly Leu Gln Glu Leu Gly Pro Gly Leu Phe Arg Gly Leu
        115                 120                 125

Ala Ala Leu Gln Tyr Leu Tyr Leu Gln Asp Asn Ala Leu Gln Ala Leu
    130                 135                 140

Pro Asp Asp Thr Phe Arg Asp Leu Gly Asn Leu Thr His Leu Phe Leu
145                 150                 155                 160

His Gly Asn Arg Ile Ser Ser Val Pro Glu Arg Ala Phe Arg Gly Leu
                165                 170                 175

His Ser Leu Asp Arg Leu Leu Leu His Gln Asn Arg Val Ala His Val
            180                 185                 190

His Pro His Ala Phe Arg Asp Leu Gly Arg Leu Met Thr Leu Tyr Leu
        195                 200                 205

Phe Ala Asn Asn Leu Ser Ala Leu Pro Thr Glu Ala Leu Ala Pro Leu
    210                 215                 220

Arg Ala Leu Gln Tyr Leu Arg Leu Asn Asp Asn Pro Trp Val Cys Asp
225                 230                 235                 240

Cys Arg Ala Arg Pro Leu Trp Ala Trp Leu Gln Lys Phe Arg Gly Ser
                245                 250                 255

Ser Ser Glu Val Pro Cys Ser Leu Pro Gln Arg Leu Ala Gly Arg Asp
            260                 265                 270

Leu Lys Arg Leu Ala Ala Asn Asp Leu Gln Gly Cys Ala
        275                 280                 285
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            20                  25                  30

Ala Ser Gln Arg Ile Phe Leu His Gly Asn Arg Ile Ser His Val Pro
        35                  40                  45

Ala Ala Ser Phe Arg Ala Cys Arg Asn Leu Thr Ile Leu Trp Leu His
    50                  55                  60

Ser Asn Val Leu Ala Arg Ile Asp Ala Ala Ala Phe Thr Gly Leu Ala
65                  70                  75                  80

Leu Leu Glu Gln Leu Asp Leu Ser Asp Asn Ala Gln Leu Arg Ser Val
                85                  90                  95

Asp Pro Ala Thr Phe His Gly Leu Gly Arg Leu His Thr Leu His Leu
            100                 105                 110

Asp Arg Cys Gly Leu Gln Glu Leu Gly Pro Gly Leu Phe Arg Gly Leu
        115                 120                 125

Ala Ala Leu Gln Tyr Leu Tyr Leu Gln Asp Asn Ala Leu Gln Ala Leu
    130                 135                 140

Pro Asp Asp Thr Phe Arg Asp Leu Gly Asn Leu Thr His Leu Phe Leu
145                 150                 155                 160

His Gly Asn Arg Ile Ser Ser Val Pro Glu Arg Ala Phe Arg Gly Leu
                165                 170                 175

His Ser Leu Asp Arg Leu Leu Leu His Gln Asn Arg Val Ala His Val
            180                 185                 190

His Pro His Ala Phe Arg Asp Leu Gly Arg Leu Met Thr Leu Tyr Leu
        195                 200                 205

Phe Ala Asn Asn Leu Ser Ala Leu Pro Thr Glu Ala Leu Ala Pro Leu
    210                 215                 220

Arg Ala Leu Gln Tyr Leu Arg Leu Asn Asp Asn Pro Trp Val Cys Asp
225                 230                 235                 240

Cys Arg Ala Arg Pro Leu Trp Ala Trp Leu Gln Lys Phe Arg Gly Ser
                245                 250                 255

Ser Ser Glu Val Pro Cys Ser Leu Pro Gln Arg Leu Ala Gly Arg Asp
            260                 265                 270
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Leu Lys Arg Leu Ala Ala Asn Asp Leu Gln Gly Cys Ala Val Ala Thr
275 280 285

Gly Pro Tyr His Pro Ile Trp Thr Gly Arg Ala Thr Asp Glu Glu Pro
290 295 300

Leu Gly Leu Pro Lys Cys Cys Gln Pro Asp Ala Ala Asp Lys Ala
305 310 315

<210> 5
<211> 284
<212> PRT
<213> Rattus norvegicus

<400> 5
Cys Pro Gly Ala Cys Val Cys Tyr Asn Glu Pro Lys Val Thr Thr Ser
1 5 10 15

Arg Pro Gln Gln Gly Leu Gln Ala Val Pro Ala Gly Ile Pro Ala Ser
20 25 30

Ser Gln Arg Ile Phe Leu His Gly Asn Arg Ile Ser Tyr Val Pro Ala
35 40 45

Ala Ser Phe Gln Ser Cys Arg Asn Leu Thr Ile Leu Trp Leu His Ser
50 55 60

Asn Ala Leu Ala Gly Ile Asp Ala Ala Ala Phe Thr Gly Leu Thr Leu
65 70 75 80

Leu Glu Gln Leu Asp Leu Ser Asp Asn Ala Gln Leu Arg Val Val Asp
85 90 95

Pro Thr Thr Phe Arg Gly Leu Gly His Leu His Thr Leu His Leu Asp
100 105 110

Arg Cys Gly Leu Gln Glu Leu Gly Pro Gly Leu Phe Arg Gly Leu Ala
115 120 125

Ala Leu Gln Tyr Leu Tyr Leu Gln Asp Asn Asn Leu Gln Ala Leu Pro
130 135 140

Asp Asn Thr Phe Arg Asp Leu Gly Asn Leu Thr His Leu Phe Leu His
145 150 155 160

Gly Asn Arg Ile Pro Ser Val Pro Glu His Ala Phe Arg Gly Leu His
165 170 175

Ser Leu Asp Arg Leu Leu Leu His Gln Asn His Val Ala Arg Val His
180 185 190

Pro His Ala Phe Arg Asp Leu Gly Arg Leu Met Thr Leu Tyr Leu Phe
195 200 205

Ala Asn Asn Leu Ser Met Leu Pro Ala Glu Val Leu Val Pro Leu Arg
210 215 220

```
Ser Leu Gln Tyr Leu Arg Leu Asn Asp Asn Pro Trp Val Cys Asp Cys
225                 230                 235                 240

Arg Ala Arg Pro Leu Trp Ala Trp Leu Gln Lys Phe Arg Gly Ser Ser
                245                 250                 255

Ser Gly Val Pro Ser Asn Leu Pro Gln Arg Leu Ala Gly Arg Asp Leu
            260                 265                 270

Lys Arg Leu Ala Thr Ser Asp Leu Glu Gly Cys Ala
        275                 280
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<210> 6
<211> 318
<212> PRT
<213> Rattus norvegicus

<400> 6

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Cys Pro Gly Ala Cys Val Cys Tyr Asn Glu Pro Lys Val Thr Thr Ser
  1               5                  10                  15

Arg Pro Gln Gln Gly Leu Gln Ala Val Pro Ala Gly Ile Pro Ala Ser
            20                  25                  30

Ser Gln Arg Ile Phe Leu His Gly Asn Arg Ile Ser Tyr Val Pro Ala
        35                  40                  45

Ala Ser Phe Gln Ser Cys Arg Asn Leu Thr Ile Leu Trp Leu His Ser
    50                  55                  60

Asn Ala Leu Ala Gly Ile Asp Ala Ala Ala Phe Thr Gly Leu Thr Leu
65                  70                  75                  80

Leu Glu Gln Leu Asp Leu Ser Asp Asn Ala Gln Leu Arg Val Val Asp
                85                  90                  95

Pro Thr Thr Phe Arg Gly Leu Gly His Leu His Thr Leu His Leu Asp
            100                 105                 110

Arg Cys Gly Leu Gln Glu Leu Gly Pro Gly Leu Phe Arg Gly Leu Ala
        115                 120                 125

Ala Leu Gln Tyr Leu Tyr Leu Gln Asp Asn Asn Leu Gln Ala Leu Pro
    130                 135                 140

Asp Asn Thr Phe Arg Asp Leu Gly Asn Leu Thr His Leu Phe Leu His
145                 150                 155                 160

Gly Asn Arg Ile Pro Ser Val Pro Glu His Ala Phe Arg Gly Leu His
                165                 170                 175

Ser Leu Asp Arg Leu Leu Leu His Gln Asn His Val Ala Arg Val His
            180                 185                 190
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Pro His Ala Phe Arg Asp Leu Gly Arg Leu Met Thr Leu Tyr Leu Phe
        195                 200                 205

Ala Asn Asn Leu Ser Met Leu Pro Ala Glu Val Leu Val Pro Leu Arg
    210                 215                 220

Ser Leu Gln Tyr Leu Arg Leu Asn Asp Asn Pro Trp Val Cys Asp Cys
225                 230                 235                 240

Arg Ala Arg Pro Leu Trp Ala Trp Leu Gln Lys Phe Arg Gly Ser Ser
                245                 250                 255

Ser Gly Val Pro Ser Asn Leu Pro Gln Arg Leu Ala Gly Arg Asp Leu
            260                 265                 270

Lys Arg Leu Ala Thr Ser Asp Leu Glu Gly Cys Ala Val Ala Ser Gly
        275                 280                 285

Pro Phe Arg Pro Phe Gln Thr Asn Gln Leu Thr Asp Glu Glu Leu Leu
    290                 295                 300

Gly Leu Pro Lys Cys Cys Gln Pro Asp Ala Ala Asp Lys Ala
305                 310                 315
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<210> 7
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 7
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Ala Ala Ala Phe Gly Leu Thr Leu Leu Glu Gln Leu Asp Leu Ser Asp
  1               5                  10                  15

Asn Ala Gln Leu Arg
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<210> 8
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 8
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Leu Asp Leu Ser Asp Asn Ala Gln Leu Arg
  1               5                  10
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<210> 9
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 9
Leu Asp Leu Ser Asp Asp Ala Glu Leu Arg
1 5 10

<210> 10
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 10
Leu Asp Leu Ala Ser Asp Asn Ala Gln Leu Arg
1 5 10

<210> 11
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 11
Leu Asp Leu Ala Ser Asp Asp Ala Glu Leu Arg
1 5 10

<210> 12
<211> 11
<212> PRT
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<400> 12
Leu Asp Ala Leu Ser Asp Asn Ala Gln Leu Arg
1 5 10

<210> 13
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 13
Leu Asp Ala Leu Ser Asp Asp Ala Glu Leu Arg
1 5 10

<210> 14
<211> 11
<212> PRT
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<220>
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<400> 14
Leu Asp Leu Ser Ser Asp Asn Ala Gln Leu Arg
1 5 10

<210> 15
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 15
Leu Asp Leu Ser Ser Asp Glu Ala Glu Leu Arg
1 5 10

<210> 16
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<400> 16
Asp Asn Ala Gln Leu Arg Val Val Asp Pro Thr Thr
1 5 10

<210> 17
<211> 6
<212> PRT
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<220>
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<400> 17
Asp Asn Ala Gln Leu Arg
1 5

<210> 18
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 18
Ala Asp Leu Ser Asp Asn Ala Gln Leu Arg Val Val Asp Pro Thr Thr
1 5 10 15

<210> 19
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 19
Leu Ala Leu Ser Asp Asn Ala Gln Leu Arg Val Val Asp Pro Thr Thr
1 5 10 15

<210> 20
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 20
Leu Asp Leu Ser Asp Asn Ala Ala Leu Arg Val Val Asp Pro Thr Thr
1 5 10 15

<210> 21
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 21
Leu Asp Leu Ser Asp Asn Ala Gln Leu His Val Val Asp Pro Thr Thr
1 5 10 15

<210> 22
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 22
Leu Asp Leu Ser Asp Asn Ala Gln Leu Ala Val Val Asp Pro Thr Thr
1 5 10 15